CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-336/21-708

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336
NDA 21-708

Melissa L. Goodhead, B.S., RAC
Director of Regulatory Affairs
Somerset Pharmaceuticals, Inc.
2202 N. West Shore Blvd., Suite 450
Tampa, FL 33607

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) 21-336, dated May 24, 2001, received May 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM™ (selegiline transdermal system) patches, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2. Please also refer to our action letter of March 25, 2002 for this application.

We acknowledge receipt of your submissions and correspondence dated:

April 4, 2002	May 14, 2002	May 21, 2002	June 26, 2002
August 1, 2002	January 29, 2003	March 13, 2002	July 31, 2003
August 7, 2003	August 12, 2003(2)	August 13, 2003	August 18, 2003(3)
August 20, 2003	Sept. 4, 2003	Sept. 9, 2003	Sept. 16, 2003
Sept 19, 2003	Sept. 25, 2003	Sept. 26, 2003	Oct. 6, 2003
Oct. 15, 2003	Oct. 27, 2003	Oct. 29, 2003 (2)	Nov. 7, 2003
Jan. 6, 2004	Jan. 15, 2004	Jan. 20, 2004	Jan. 23, 2004 (2)

We also refer to meetings and teleconferences which have taken place between representatives of your firm and this Agency on May 2, 2002, June 5, 2002, August 16, 2002, August 20, 2002, October 4, 2002, February 24, 2003, March 28, 2003, August 20, 2003, October 3, 2003, and October 8, 2003.

We note that your July 31, 2003 submission constituted a complete response to our March 25, 2002 action letter.

In addition, we refer to your New Drug Application NDA 21-708, dated October 15, 2003, received October 16, 2003. We note the administrative creation of this NDA to address the maintenance treatment of major depressive disorder, with the acute treatment indication retained under the existing NDA 21-336.

We have completed our review of your new drug applications as amended, and have concluded that both applications are approvable. Before these applications may be approved, however, it will be necessary for you to respond to the following comments and/or requests. These comments / requests pertain to both NDAs unless otherwise indicated, and a single response with appropriate cross-reference may be submitted to address the issues for both applications.

Proprietary Name (EMSAM) Review and Related Labeling Comments

1. Your proposed proprietary name, EMSAM, is acceptable to the Agency at this time. We remind you that this proprietary name will need to be re-evaluated approximately three months (90 days) prior to the expected approval of this application.
2. We have the following recommendations with respect to the container label and carton labeling:

General Comments:

- Modify the layout of the pouch and patch label and carton labeling, so that each product strength (20 mg, 30 mg, 40 mg) is distinguishable from the others (i.e., contrasting color, boxing, or other means).
- In some sections, the contents are described as '
  . Please revise content descriptions to maintain consistency.
- Please add a statement to the labeling which describes the release rate for the patch (amount of drug released per 24 hours). This should be done for each dosage strength.

Patch label (peel-off backing):

- Please see the first bullet point under *General Comments* above.
- Please increase the prominence of the product strength on the patch labels so that it is more visible (contrasting colors, boxing, etc.). The strength is presently stated in fine print beneath the proprietary name.

Pouch Label:

- Please see above comments (*General* and *Patch label*).
- Please include an "Rx only" statement on the pouches.
- We note your proposal to market the product in boxes of 30 patches. It is unclear whether the unit dose package is child resistant. We recommend the addition of the following statement: "This unit dose package is not child resistant."
- The net quantity is located in close proximity to the product strength, which may be confusing. Please relocate the net quantity away from the product strength and remove the blue horizontal line which embeds the net quantity text.
- If space permits, we recommend the addition of pictures to the INSTRUCTIONS FOR APPLICATION to minimize patient confusion.

Carton Labeling:

- Please see all above comments.
- The net quantity is located in close proximity to the product strength, which may be confusing, particularly in the case of the net quantity of 30 of the 30 mg patches. Please relocate the net quantity away from the product strength and remove the blue horizontal line which embeds the net quantity text.

Nonclinical Pharmacology and Toxicology

1. After completing our review of the 78-week mouse and the 104-week rat dietary carcinogenicity studies, we have concluded that additional assessment of the carcinogenic potential of transdermal selegiline will be required. This conclusion is based on three factors: (1) the inadequacy of the dietary carcinogenicity studies as conducted, (2) the inadequacy of the plasma exposures for selegiline achieved in the carcinogenicity studies relative to expected plasma exposure in human at the transdermal maximum recommended human dose (MRHD, 40 mg/day), (3) the inadequacy of dietary studies to assess tumorigenic effects at the site of application (skin). In both the mouse and rat studies, a maximum tolerated dose

was achieved; however, the only dose-limiting effect was on body weight. The high doses produced excessive decreases in body weight relative to controls. Such effects on body weight have been demonstrated to reduce sensitivity of the animals to develop spontaneous and drug-induced tumors. And, in the carcinogenicity studies, there were decreases in overall tumors at the high dose, and no significant increases in any tumor type at any dose in either males or females. Thus, there is concern that the studies are insensitive tests of carcinogenic potential. The short duration of the mouse study (78-week instead of 2-year) increases our concern regarding the insensitivity of that study. Also, an incomplete battery of tissues was examined in both the mouse and rat studies (missing tissues include duodenum, jejunum, cecum, nasal cavity, eye, seminal vesicles, spinal cord).

The adequacy of the systemic exposures achieved in the carcinogenicity studies has previously been discussed with you. Although we informed you (pre-NDA meeting on March 28, 2001) that this issue had been adequately addressed, the fact that you are now proposing to market higher doses of EMSAM (i.e., 30 and 40 mg) than originally proposed (i.e., 20 mg) required us to revisit this issue. The transdermal route results in a greater selegiline-to-metabolite ratio than the oral route in both animals and humans. Based on available data, plasma selegiline levels in humans at the transdermal MRHD are 14 times higher than at the oral dose (5 mg b.i.d.) approved for treatment of Parkinson's disease. Estimating from plasma exposure data provided in a 14-day dietary bridging study in rat (at the high dose used in the 104-week study), plasma levels of selegiline achieved at the mid dose in the 104-week study were ≈0.04-0.2 times the plasma selegiline levels at the transdermal MRHD. A pharmacokinetic bridging study in mouse was requested, but was never received. Therefore, plasma exposure to selegiline and metabolites cannot be estimated for the 78-week mouse study.

Regarding local effects, dietary studies do not address the potential for tumorigenic effects at the site of application of a transdermal formulation since exposure to drug at the application site (in this case, skin) would be expected to far exceed that obtained with oral dosing.

We believe that the 104-week rat study provides an adequate assessment of the systemic carcinogenic potential of the metabolites, N-desmethylselegiline, l-amphetamine, and l-methamphetamine. The mid-dose did not produce an excessive body weight effect and was associated with plasma exposure to metabolites fairly similar to that expected at the transdermal MRHD. However, neither of the dietary carcinogenicity studies provides an adequate assessment of the carcinogenic potential of selegiline, either systemically or at the site of application. The fact that selegiline was mutagenic and clastogenic in an *in vitro* mouse lymphoma tk assay, with and without metabolic activation, and that EMSAM in intended for use in a young, relatively healthy population heightens the need for additional testing. Therefore, you need to conduct a 2-year carcinogenicity study in the mouse using the dermal route. This requirement is predicated, in part, on the assumption that higher plasma exposure to selegiline can be obtained in the mouse with dermal application, and at doses that do not have excessive effects on body weight. As previously noted, no plasma exposure data are available in mouse. However, in a 6-month study in rat, notably higher plasma levels of selegiline appear to have been achieved (without excessive effects on body weight) with transdermal than with oral dosing at the high dose used in the 2-yr oral carcinogenicity study.

2. The *in vivo* micronucleus assay in mouse (Study No. 23770-0-455OECD) was conducted using the oral route. In animals and human, circulating levels of selegiline relative to metabolites (i.e., the selegiline-to-metabolite ratios) are notably higher following transdermal as compared to oral dosing. Therefore, there is a concern that plasma exposure to selegiline, in particular, in the *in vivo* assay was not adequate to cover the expected human plasma exposure. You have not provided pharmacokinetic/toxicokinetic data in the mouse that would allow for an estimate of plasma exposure to selegiline and metabolites. You need to either justify the use of the oral route in the *in vivo* assay or conduct a repeat *in vivo* micronucleus assay using a route that would result in higher circulating levels of selegiline.

3. In order for us to complete our evaluation of the submitted nonclinical data, you need to provided the following information: (a) clarification on the meaning of the abbreviation "TA" in the histopathology tumor data listings and (b) verification that the toxicokinetic data in Table 2 from the 6-month toxicity study in rat, designated as "Selegiline Composite", refers to PK parameters of the parent compound alone.

4. Further comments from our nonclinical pharmacology and toxicology review have been incorporated as modifications to language in the attached draft labeling. This draft labeling is derived from the labeling included in your July 31, 2003 resubmission. Please see our comments under the heading "**Labeling (Package Insert and Container Labeling"** below.

Chemistry, Manufacturing and Controls

1. Include, as part of the drug product release specifications, a for determining the of selegiline. Please include a copy of the drug product method and validation results in your complete response to this letter.

2. We note that your specified impurities are suspected mutagens. Ideally, these impurities should not be present; however, if elimination is not possible, you need to reduce the amount of each impurity to a level not to exceed . This limit was chosen, in part, based on the ICH Q3C guidance on residual solvents (Guidance for Industry, Q3C Impurities: Residual Solvents, December 1997) which establishes a limit of 2 ppm for benzene, a known human carcinogen, and establishes limits of 4 to 8 ppm for several compounds labeled as possible or probable human carcinogens.

   You must demonstrate that the amount of each of these potential mutagenic compounds does not exceed Lowering the level for each of these impurities to less than would be preferable if the methodologies exist. Provide details of the method(s) [including limits of detection (LOD) and quantitation (LOQ)] used to evaluate the level of each impurity. Alternatively, you could determine the genotoxic potential of by directly testing these compounds in an *in vitro* gene mutation assay in bacteria (Ames test) and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing). These data would then be taken into consideration, in conjunction with other available data (e.g., published literature), in determining the need to lower the levels of these impurities.

Clinical Pharmacology and Biopharmaceutics

1. Please adopt the following dissolution method and specifications as the regulatory method. This method and specifications incorporates the specifications previously found acceptable for the 20 mg patch.

Formulation(s)	20 mg / 20 cm^2 and 30 mg / 30 cm^2	40 mg / 40 cm^2
Media	0.1 M Potassium Phosphate Buffer Monobasic pH 5	0.1 M Potassium Phosphate Buffer Monobasic pH 5
Volume	500 ml	***1000 ml***
Temp (°C)	32 ± 0.5	32 ± 0.5
Apparatus	USP 5 Paddle over disk	***USP 6 Rotating Cylinder***
RPM	50	50
Sampling Times And Specifications (% LC)	1 hr 4 hr 8 hr 24 hr NLT	1 hr 4 hr 8 hr 24 hr NLT
Acceptance Criteria	Per acceptance table 4 in TRANSDERMAL DELIVERY SYSTEMS—GENERAL DRUG RELEASE STANDARDS USP 26-NF 21 2nd Suppl., section<724> DRUG RELEASE	

2. Further comments from our clinical pharmacology and biopharmaceutics review have been incorporated as modifications to language in the attached draft labeling. This draft labeling is derived from the labeling included in your July 31, 2003 resubmission. Please see our comments under the heading "**Labeling (Package Insert and Container Labeling**" below.

3. We request that you examine the following three issues as Phase 4 commitments and commit to submitting study reports for them; please propose time frames for the submission of the reports following approval of the NDAs. Reports should be submitted to NDA 21-336, with letters of cross-reference submitted to NDA 21-708, assuming both NDAs are approved concurrently.

- ***ISSUE 1: Adhesion.*** Please provide information regarding the adhesion properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:
  - Subject age [i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85)].
  - Application to the different labeled application sites including the upper torso and upper arm.
  - For each study arm 100 completers are anticipated.
  - The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

- ***ISSUE 2: Dermal Tolerability.*** Please provide information regarding the dermal tolerability of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

• Subject age [- i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85).
• Application to the different labeled application sites including the upper torso and upper arm.
• For each study arm 100 completers are anticipated.
• The data generated should also be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

- ***ISSUE 3: Performance of Selegiline Transdermal Systems in the Elderly.*** Only 3 subjects studied were > 65 years of age. All three were women and the eldest was 70 years old. Consequently, please provide information regarding the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), in young healthy adults, the elderly (i.e. 65 – 84 y ears old), and the extreme elderly (i.e.> 85).
  • The effects of gender and ethnicity/race should be examined for each age range.
  • Information provided for each age group should include:
    • complete pharmacokinetic profiles of selegiline and the 3 metabolites previously examined,
    • the tyramine response,
    • MAO selectivity,
    • drug delivery, and
    • safety information by age.
  • With regard to safety we are specifically interested in CNS effects, as well as differences in blood pressure changes, especially as the elderly typically have higher baseline systolic blood pressure and are at risk for orthostatic hypotension.

Clinical / Statistical / Clinical Safety
We believe that you have now submitted sufficient data to support the efficacy of the selegiline transdermal system in the acute and maintenance treatment of major depressive disorder as presented in the attached draft labeling. This draft labeling is derived from the labeling included in your July 31, 2003 resubmission. It addresses safety issues identified during our review, such as the potential reaction to concomitantly ingested tyramine ("cheese reaction"), postural hypotension, the potential for sexual dysfunction, and the risk of serotonin syndrome. Please see our further comments under the heading **"Labeling (Package Insert and Container Labeling"** below.

Request for Regulatory Update and Foreign Labeling
Please provide any new information on the regulatory status of EMSAM worldwide. We require a review of the status of all actions with regard to this drug, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we also ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. It is only necessary to provide information that is more recent than that provided in your July 31, 2003 Complete Response.

In addition, we request that you provide us with any current foreign labeling (package inserts) for EMSAM, with English translations where needed.

Request for Safety Update and World Literature Update

Also, in your response to this letter, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b).

1. The safety update should include data from all non-clinical and clinical studies of EMSAM, regardless of indication, dosage form, or dose level.
2. Please describe in detail any significant changes or findings in the safety profile.
3. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, please incorporate new safety data as follows:
    - Present new safety data from the studies for the proposed indications using the same format as used in your July 31, 2003 Complete Response.
    - Present tabulations of the new safety data combined with the data from the Complete Response.
    - Include tables that compare frequencies of adverse events in the Complete Response with the retabulated frequencies described in the preceding bullet point.
4. For indications other than the proposed indications, provide separate tables for the frequencies of adverse events occurring in clinical trials.
5. Please present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
6. Please provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, please provide narrative summaries for serious adverse events.
7. Please describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the Complete Response data.
8. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of EMSAM. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of EMSAM. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling (Package Insert and Container Labeling)

In addition to responding to the points listed above, it will be necessary for you to submit final labeling revised as shown in the attachment to this letter. We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of EMSAM (selegiline transdermal system) in the acute and maintenance treatment of MDD. You will see that we have proposed a number of changes to the draft labeling submitted in your July 31, 2003 Complete Response, and explanations for these changes are generally provided in the bracketed comments embedded within the proposed text. Please use the proposed text verbatim, with the exception of revisions in response to comments embedded in the text or presented in this letter.

Division staff are willing to discuss this revised labeling in detail and to meet with you to resolve any disagreements you may have with the proposed labeling.

To facilitate re-review of your proposed proprietary name, please also include three full sets of container, carton and blister labeling mockups for all dosage strengths and packaging configurations, as well as mockups to scale of your proposed package insert, in your complete response to this letter.

Promotional Materials
In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than in final printed format.

Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Options Under 21 CFR 314.110
Within 10 (ten) days after the date of this letter, you are required to amend the applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65.

Any amendments should respond to all of the deficiencies listed. A Complete Response to NDA 21-336 may be incorporated by cross-reference into NDA 21-708 so long as it addresses the deficiencies relevant to that NDA. We will not process a partial reply as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Opportunity for Informal Meeting Under 21 CFR 314.102(d)
Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division, to discuss what further steps need to be taken before the applications may be approved.

This drug product may not be legally marketed in the dosage form and for the indications submitted under these NDAs until you have been notified in writing that this application has been approved.

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research